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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,407	12/08/2006	Takumi Teratani	701053	2167

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LEYDIG VOIT & MAYER, LTD
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO, IL 60601-6731

EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,407	TERATANI ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30 and 32-34* is/are pending in the application.

4a) Of the above claim(s) *1-7,14-30 and 32-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/19/07;12/28/07;9/2/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-30 and 32-34 are pending in the present application.

Applicant's election without traverse of Group II (claims 8-13) in the reply filed on 5/8/09 is acknowledged.

Accordingly, claims 1-7, 14-30 and 32-34 are withdrawn from further consideration because they are directed to non-elected inventions.

Claims 8-13 are examined on the merits herein.

Claim Objections

Claims 12 and 13 are objected to because of the term "rLIF". This abbreviation should be spelled out in full at the first occurrence of the term.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the limitations "under **the** culture conditions" in line 2, "**the** culture of rat blastocysts" in line 4, and "the culture of the dissociated inner cell mass" in step (B) of the claim. There is insufficient antecedent basis for these limitations in the claim. This is because prior these limitations, there is no recitation of any culture conditions,

any culture of rat blastocysts or any culture of the dissociated inner cell mass. Additionally, which specific "the culture conditions", "the culture of rat blastocysts" and "the culture of the dissociated inner cell mass" do Applicants refer to? Clarification is requested because the metes and bounds of the claim as written are not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8 and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Vassilieva et al. (Experimental Cell Research 258:361-373, 2000; IDS).

Vassilieva et al already disclosed a method for establishment of SSEA-1- and Oct-4-expressing rat embryonic stem-like cell lines, said method comprises: (a) culturing rat embryos at blastocyst stage onto mitomycin C inactivated mouse primary embryonic fibroblasts in 0.1% gelatine-treated wells of four-well tissue-culture plates and forming embryonal out growths; (b) undifferentiated cells of embryonal outgrowths (inner cell mass cells) were mechanically disaggregated using glass pipettes and aggregates of 20-50 cells were seeded onto fresh feeder cells; and (c) colonies representing typical morphology of compacted ES cells were selected and passaged every day by mechanical disaggregation, and when ES-like colonies reached higher

density they were transferred to 35- and 60-mm tissue culture dishes and the cultivation medium used was DMEM,ISCOVE supplemented with 15% of fetal calf serum and basic additives including 20 ng/ml human LIF (see at least the abstract and particularly the section "Establishment of rat ES-like cell lines" on page 362 and col. 1 of page 363 and Table 1). All of the established rat embryonic stem-like (RES) cell lines showed ALP staining, with the morphology of RES-1 and RES-15 cells closely resembled those of mouse ES cells and they express Oct-4 and SSEA-1 (Table 1).

Since the term "substantially serum free" is defined in the present application to mean not to contain serum in an amount that rat ES cell loses the properties as an ES cell (e.g., becomes negative for alkaline phosphatase activity) due to the effect of serum (page 17, lines 18-22), the above teachings of Vassilieva et al meet every limitation of the claims as written.

Therefore, the reference anticipates the instant claims.

Claims 8, 10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Loring, J. (WO 99/27076; IDS).

Loring already disclosed at least a method for obtaining non-mouse embryonic stem cells, including rat embryonic stem cells, said method comprises: (a) culturing harvested blastocysts or delayed-blastocysts in individual wells of a 24-well plate in any appropriate medium under any conditions which allow for growth and proliferation of ES cells, with an exemplified medium is DMEM with glutamine and high glucose supplemented with 15% fetal bovine serum, !X non-essential amino acids, 0.1 mM 2-

mercaptoethanol and antibiotics; (b) the inner cell mass (ICM) was removed under conditions that minimize contamination with other cell types after about 3 to 5 days in culture using a micropipette and then dissociated with 0.25% trypsin, under which conditions the ICM is dispersed either to a single cell suspension or **more preferably to produce small groups of cells**; (c) ICM cultures were cultured in 6 well dishes and colonies arising from the dispersed ICMs will be selected by morphology criteria with exogenous growth factors such as LIF, bFGF and SCF alone or in combination may be added to the cultures or ICM cultures were cultured on a feeder layer; (d) after about a week of culture, colonies that resembled ES cells were dissociated and sub-cultured; (e) the sub-cultured ES cells were passed once to obtain cell lines BNRB-1 and FRDB-1 which are AP positive; and (e) the rat cell lines were co-cultured with mouse ES cells to obtain pluripotent rat ES cells which differentiated into a number of morphologically different cell types and embryoid bodies, including the ability of making a transgenic rat (see at least the abstract; pages 11-13; particular example 2, page 26, lines 7-8; examples 4-6).

Since the term "substantially serum free" is defined in the present application to mean not to contain serum in an amount that rat ES cell loses the properties as an ES cell (e.g., becomes negative for alkaline phosphatase activity) due to the effect of serum (page 17, lines 18-22), the above teachings of Loring, J. meet every limitation of the claims as written.

Therefore, the reference anticipates the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Vassilieva et al. (Experimental Cell Research 258:361-373, 2000; IDS) or Loring, J. (WO 99/27076; IDS). in view of Takahama et al. (Oncogene 16:3189-3196, 1998; IDS).

Vassilieva et al already disclosed a method for establishment of SSEA-1- and Oct-4-expressing rat embryonic stem-like cell lines, said method comprises: (a) culturing rat embryos at blastocyst stage onto mitomycin C inactivated mouse primary embryonic fibroblasts in 0.1% gelatine-treated wells of four-well tissue-culture plates and forming embryonal out growths; (b) undifferentiated cells of embryonal outgrowths

(inner cell mass cells) were mechanically disaggregated using glass pipettes and aggregates of 20-50 cells were seeded onto fresh feeder cells; and (c) colonies representing typical morphology of compacted ES cells were selected and passaged every day by mechanical disaggregation, and when ES-like colonies reached higher density they were transferred to 35- and 60-mm tissue culture dishes and the cultivation medium used was DMEM,ISCOVE supplemented with 15% of fetal calf serum and basic additives including 20 ng/ml human LIF (see at least the abstract and particularly the section "Establishment of rat ES-like cell lines" on page 362 and col. 1 of page 363 and Table 1). All of the established rat embryonic stem-like (RES) cell lines showed ALP staining, with the morphology of RES-1 and RES-15 cells closely resembled those of mouse ES cells and they express Oct-4 and SSEA-1 (Table 1).

Loring already disclosed at least a method for obtaining non-mouse embryonic stem cells, including rat embryonic stem cells, said method comprises: (a) culturing harvested blastocysts or delayed-blastocysts in individual wells of a 24-well plate in any appropriate medium under any conditions which allow for growth and proliferation of ES cells, with an exemplified medium is DMEM with glutamine and high glucose supplemented with 15% fetal bovine serum, !X non-essential amino acids, 0.1 mM 2-mercaptoethanol and antibiotics; (b) the inner cell mass (ICM) was removed under conditions that minimize contamination with other cell types after about 3 to 5 days in culture using a micropipette and then dissociated with 0.25% trypsin, under which conditions the ICM is dispersed either to a single cell suspension or **more preferably to produce small groups of cells**; (c) ICM cultures were cultured in 6 well dishes and

colonies arising from the dispersed ICMs will be selected by morphology criteria with exogenous growth factors such as LIF, bFGF and SCF alone or in combination may be added to the cultures or ICM cultures were cultured on a feeder layer; (d) after about a week of culture, colonies that resembled ES cells were dissociated and sub-cultured; (e) the sub-cultured ES cells were passed once to obtain cell lines BNRB-1 and FRDB-1 which are AP positive; and (e) the rat cell lines were co-cultured with mouse ES cells to obtain pluripotent rat ES cells which differentiated into a number of morphologically different cell types and embryoid bodies, including the ability of making a transgenic rat (see at least the abstract; pages 11-13; particular example 2, page 26, lines 7-8; examples 4-6).

It should be noted that the term "substantially serum free" is defined in the present application to mean not to contain serum in an amount that rat ES cell loses the properties as an ES cell (e.g., becomes negative for alkaline phosphatase activity) due to the effect of serum (page 17, lines 18-22).

,Neither Vassilieva et al nor Loring taught specifically the use of rat LIF-containing culture medium in step (B)-(D).

At the effective filing date of the present application, Takahama et al already cloned cDNA encoding a rat LIF and demonstrated that **culture supernatant of the rat LIF cDNA-transduced rat fibroblast cell line could maintain the stem-cell phenotype of rat ES cells which showed alkaline phosphatase activity, and this effect was much stronger than that by murine LIF** (see at least the abstract). Takahama et al specifically taught that the availability of rat LIF cDNA will assist the

establishment of in vitro culture conditions of rat ES cells and maintaining these cells in an undifferentiated state (page 319, col. 1).

It would have been obvious for an ordinary skilled artisan to modify the method of either Vassilieva et al or Loring by using rat LIF instead of human LIF or LIF derived from other species in the culture medium for establishment of rat embryonic stem-like cell lines or pluripotent rat embryonic stem cells in light of the teachings of Takhama et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because rat LIF has been shown by Takahama et al to be effective in maintaining the stem cell phenotype of rat ES cells which showed alkaline phosphatase activity, and its effect is much stronger than that of murine LIF.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of either Vassilieva et al. or Loring together with Takahama et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Vassilieva et al. (Experimental Cell Research 258:361-373, 2000; IDS) or Loring, J. (WO 99/27076; IDS) in view of Price et al. (WO 98/30679; IDS).

The teachings of Vassilieva et al and Loring were presented above. However, none of these references teaches specifically the use of a culture medium comprising a serum replacement reagent.

At the effective filing date of the present application, Price et al already taught **the use of a serum replacement medium to support the growth of embryonic stem cells in culture to avoid many problems associated with the use of serum as well as time consuming pre-screening process of serum** (see at least the abstract; Summary of the Invention, page 3, second and third paragraph; and examples).

It would have been obvious for an ordinary skilled artisan to modify the method of either Vassilieva et al or Loring by also using a serum replacement medium for establishment of rat embryonic stem-like cell lines or pluripotent rat embryonic stem cells in light of the teachings of Price et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the use of a serum replacement medium to support the growth of embryonic stem cells in culture avoids many problems associated with the use of serum as well as time consuming pre-screening process of serum as taught by Price et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of either Vassilieva et al. or Loring together with Price et al., coupled with a high level of skill of an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

1. Ueda et al (PLos One, Volume 3, Issue 7, e2800, pages 1-9, 2008) disclosed a method for establishment of rat embryonic stem cells and making of chimera rats**. It is noted that the authors of this post-filing article includes the names of both inventors of the present application (Takumi Teratani and Takahiro Ochiya)**. **Although the disclosed method for establishment and maintenance of rat ES cell lines is the same as that of the present application,** and the reported established rat embryonic stem cells are substantial similar to rat embryonic stem cells of the present application, it is noted that for some unknown reasons **unlike the rat embryonic stem cells described by the present application as well as known human ES and murine ES cells, rat embryonic stem cells of Ueda et al are negative for alkaline phosphatase** (page 5, col. 1, third paragraph).

2. Buehr et al (Cell 135:1287-1298, 2008) disclosed the preparation of "authentic" rat embryonic stem cells. With respect to the rat embryonic stem cells of Ueda et al, Buehr et al stated "A recent report claims derivation of rat ES cells in conventional ES cell cultures with feeders, LIF, and serum (Ueda et al., 2008). However, consistent with many previous reports **we find that these conditions are not adequate to drive or maintain rat ES cells. Furthermore, the cell-surface and marker profile reported by Ueda and colleagues are inconsistent with ES cell**

identity and suggest that their cells may be EpiSC like" (page 1295, col. 1, last line continues to first paragraph of col. 2).

3. Li et al. (Cell Research 19:173-186, 2009) disclosed derivation and transcriptional profiling analysis of pluripotent stem cell lines from rat blastocysts. Li et al also stated various short-comings of rat ES cell lines reported by Ueda et al (see page 163, col. 2, last paragraph continues to first paragraph of col. 1 on page 194).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/QUANG NGUYEN/
Primary Examiner, Art Unit 1633